



Center for Biologics Evaluation and Research

Electronic Submission Program

Working Instructions for Regulatory Correspondence

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1 INTRODUCTION

1.1 PROJECT OVERVIEW

The Center for Biologics Evaluation and Research (CBER) regulates and oversees the safety and efficacy of the nation's blood supply, including plasma and other blood products, and biological and biotechnology products derived from living cells. CBER receives and reviews thousands of submissions from regulated industry and consumers. These submissions include Biologics License Applications (BLAs), Investigational New Drugs (INDs), 510(k)s, Pre-market Approvals (PMAs), New Drug Applications (NDAs), lot release protocols, and adverse event reports.

CBER's goals for the review of these submissions changed with the passing of the Prescription Drug User Fee Act (PDUFA) II and the Food and Drug Administration (FDA) Modernization Act (FDAMA). These acts mandated that CBER have the capability to receive all types of regulatory submissions electronically by the year 2002. The acts also mandated expedited review of license applications and INDs. To fulfill these mandates, the agency created the Electronic Submissions Program (ESP).

The ESP project consists of the Electronic Document Room (EDR) and Electronic Secure Messaging (ESM). The EDR provides an electronic archive of regulatory submissions, with capabilities to conduct internal electronic routing, search, download, and create submission favorites lists. ESM enables Industry to submit electronic amendments via e-mail, submit PDF forms with digital signatures, as well as provides Industry and CBER a secure medium to communicate.

1.2 OBJECTIVE

The purpose of this document is to provide Industry participants with instructions for sending Regulatory Correspondence to CBER via secure e-mail. This document supports the Secure Messaging Pilot Industry Participation Document.

2 PRELIMINARY ACTIVITIES

The following section identifies the preliminary activities that Industry participants in the CBER ESM program must complete before sending a Regulatory Correspondence via ESM to CBER. The use of Tumbleweed Messaging Management Server (MMS), Virtual Private Network (VPN), or Secure Multipart Internet Mail Extensions (S/MIME) technology will be accepted.

2.1 EXCHANGING CERTIFICATES (PUBLIC KEYS)

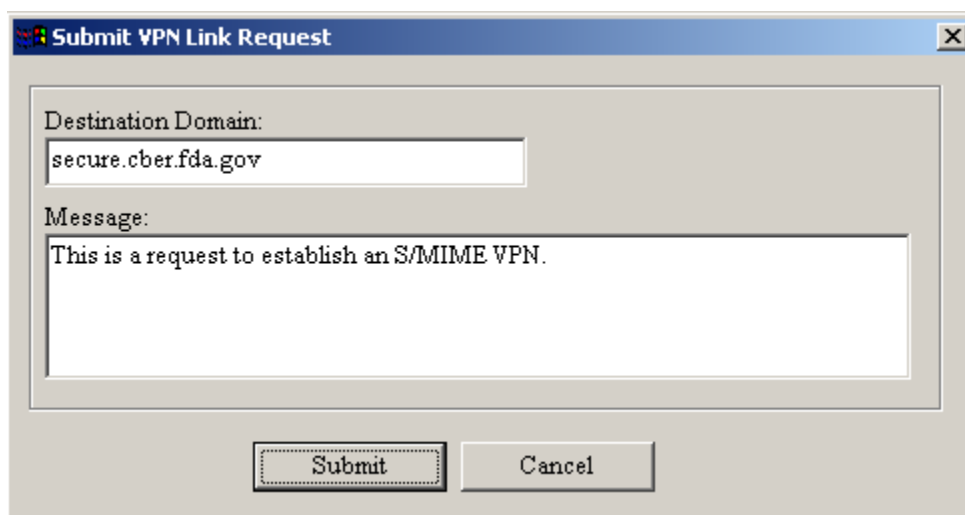
Prior to sending a Regulatory Correspondence via ESM, a certificate exchange of public keys must take place. Public Keys, also known as digital security certificates, allow multiple parties to communicate securely amongst themselves by providing signature and encryption mechanism to their messages. There are a multitude of different technologies and providers for digital certificates. The CBER MMS server employs Tumbleweed MMS VPN technology.

The following describes how the certificate exchange is accomplished by using either VPN to VPN or S/MIME to VPN technology. **Please contact Michael Fauntleroy at (301) 827-5132 before beginning the following activities.**

2.1.1 Using VPN

In order to establish a VPN link connection with CBER using MMS VPN technology, an email request must be made to the **secure.cber.fda.gov** email domain using Tumbleweed MMS. Figure 2.1.1-1 depicts submitting a VPN request using Tumbleweed MMS to the CBER MMS server.

Figure 2.1.1-1-VPN Request



Submit VPN Link Request

Destination Domain:
secure.cber.fda.gov

Message:
This is a request to establish an S/MIME VPN.

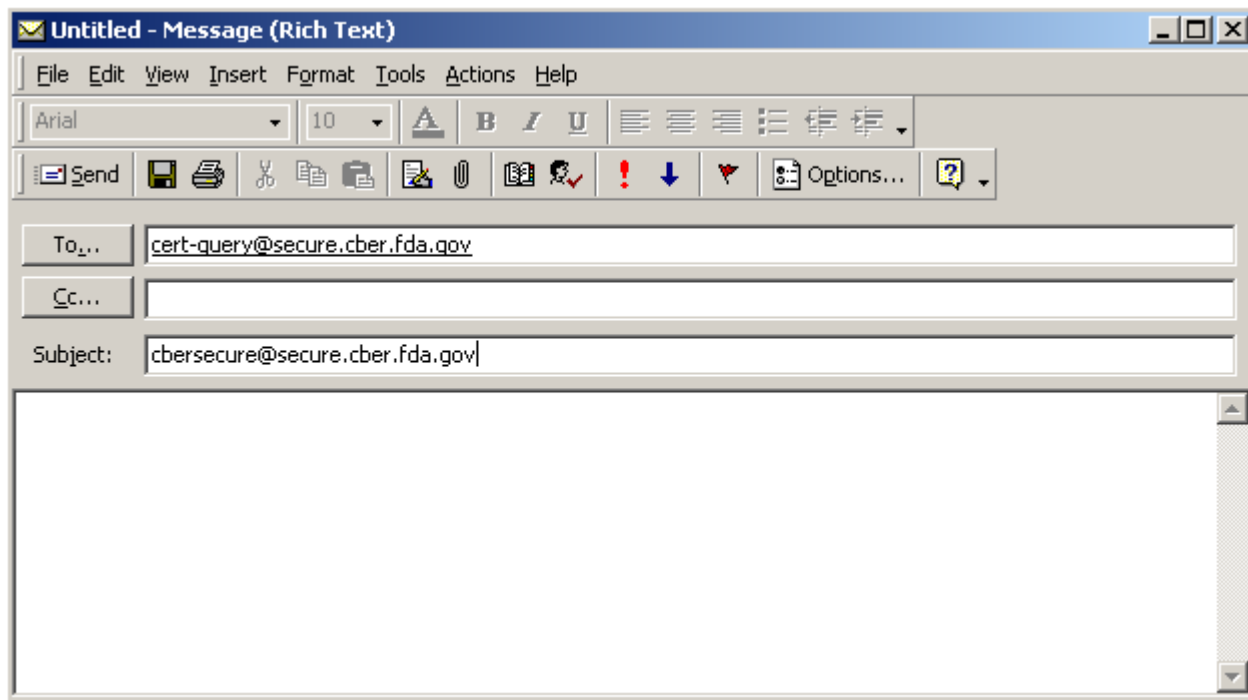
Submit Cancel

2.1.2 Using S/MIME

This document uses Microsoft Outlook 2000 images for all figures referenced. Please see your specific product documentation on S/MIME if not using Microsoft Outlook 2000. The following identifies steps required to establish an S/MIME connection with the CBER MMS server:

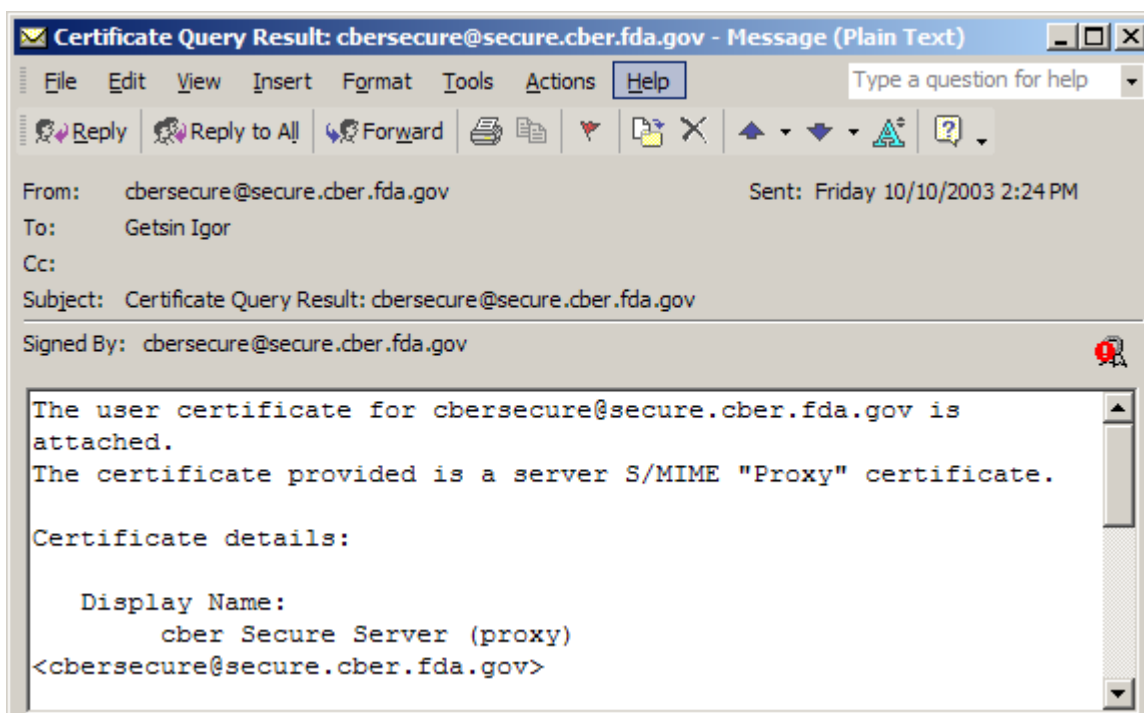
1. **Generate certificate** – For email encryption, generate or obtain a certificate from a Certificate Authority (CA) (e.g. Verisign, Entrust, and Baltimore).
2. **Send message** – In the **To:** field of the email message header, type cert-query@secure.cber.fda.gov. In the **Subject:** field of the message header, type the following - cbersecure@secure.cber.fda.gov. The message body should not contain any content. Figure 2.1.2-1 depicts a sample S/MIME request to the CBER MMS server.

Figure 2.1.2-1- Sample S/MIME Request



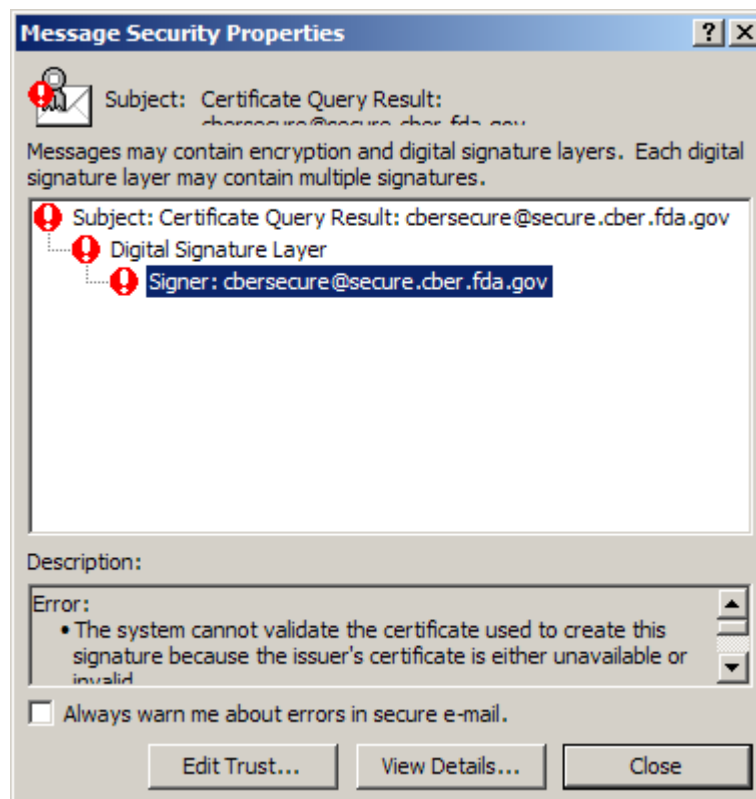
3. **Receive CBER MMS Certificate** – An automatically generated reply from cbersecure@secure.cber.fda.gov will contain the CBER MMS Certificate. Figure 2.1.2-2- depicts a sample reply message with the certificate query result.

Figure 2.1.2-2- Certificate Query Result Message



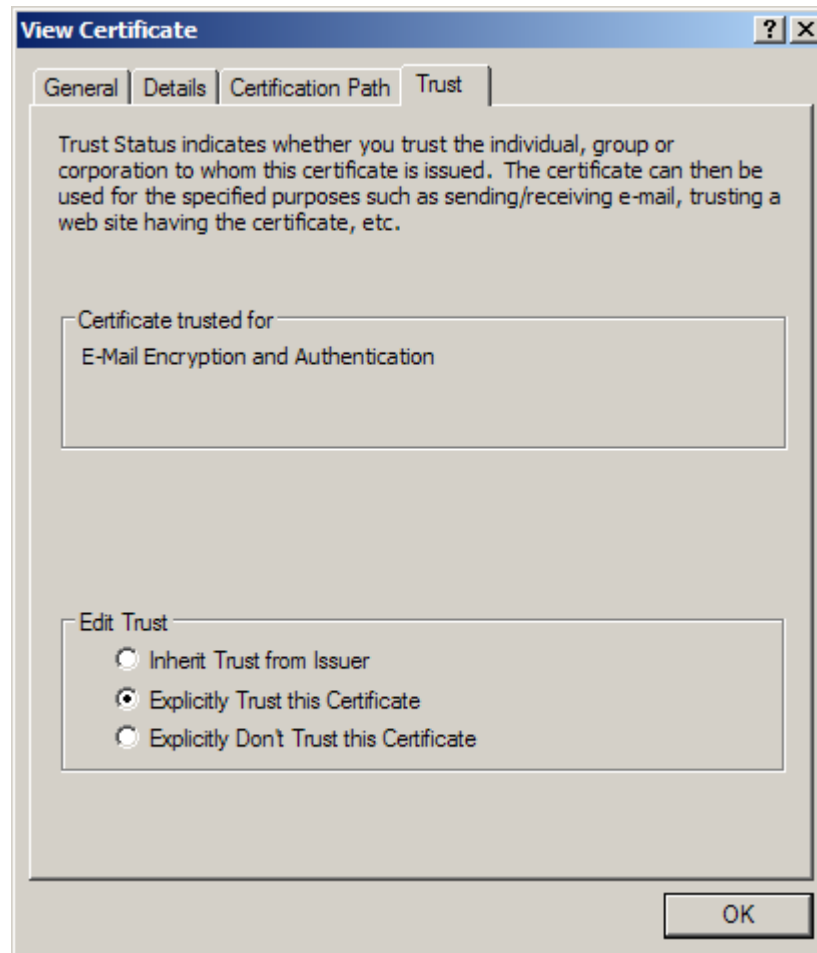
4. **Add the CBER MMS Certificate to the trusted list** – Once an email from cbersecure@secure.cber.fda.gov with the certificate is received, proceed with the steps outlined below to add the certificate to the trusted list:
 - a. Click on the **Certificate** icon (Red with Exclamation Mark [!]). Figure 2.1.2-3- depicts a **Certificate Security** dialog box.

Figure 2.1.2-3- Certificate Security dialog box



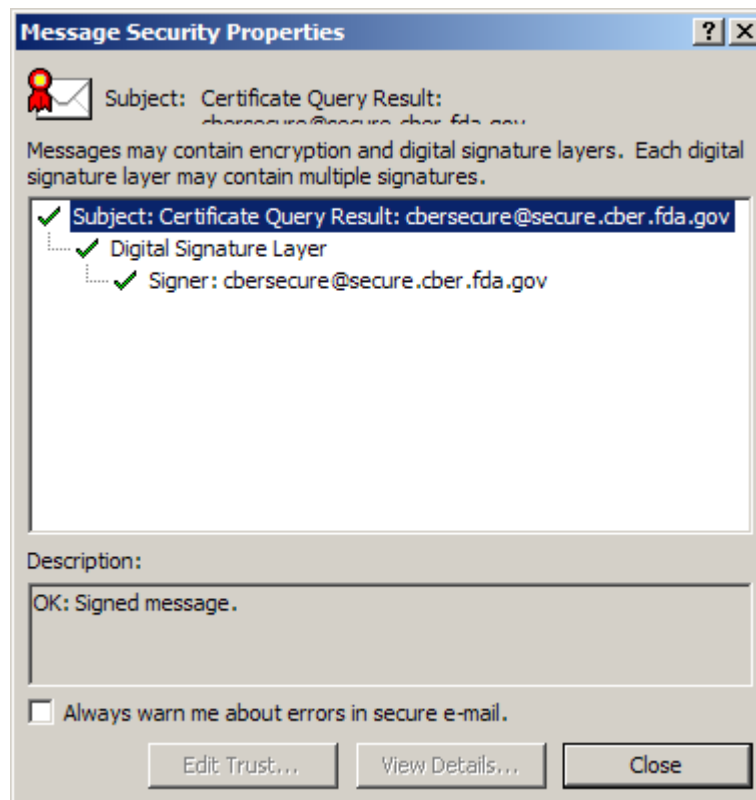
- b. Click on the **Edit Trust** button and select the **Trust** tab. Select the **Explicitly Trust this Certificate** radio button. Figure 2.1.2-4- Depicts a **Trust Edit** dialog box.

Figure 2.1.2-4- Trust Edit dialog box



- c. Click **OK** button on the **Trust Edit** dialog box. Click **Close** on the **Certificate Security** dialog box. Click on the **Certificate** icon (as specified in step a.). Figure 2.1.2-5- depicts a resulting **Certificate Security** dialog box after the trust has been established.

Figure 2.1.2-5- Certificate Security dialog box





3 SENDING THE SECURE MESSAGE

Submitting a Regulatory Correspondence requires completing the steps described in this section. Regulatory Correspondence messages may have attachments; however, there are exceptions (see Section 3.2). CBER automatically processes Regulatory Correspondence submitted via ESM; therefore, it is very important that the instructions below are followed when submitting Regulatory Correspondence via ESM. Any deviations may prevent the Regulatory Correspondence from being accepted by CBER.

3.1 OUTLINE OF STEPS

The following identifies the steps needed to create and send a Regulatory Correspondence via ESM:

1. Create an email message to send to CBER (See Section 3.1.1).
2. Type the cover page information attributes (See Section 3.1.2).
3. Type the Regulatory Correspondence below the cover page information in the body of the email message (See Section 3.1.3).
4. Attach all of the accompanying files. (See Section 3.2 for exceptions).
5. Encrypt and send the email message to the cbersecure@secure.cber.fda.gov mailbox (See Section 2.1.4).

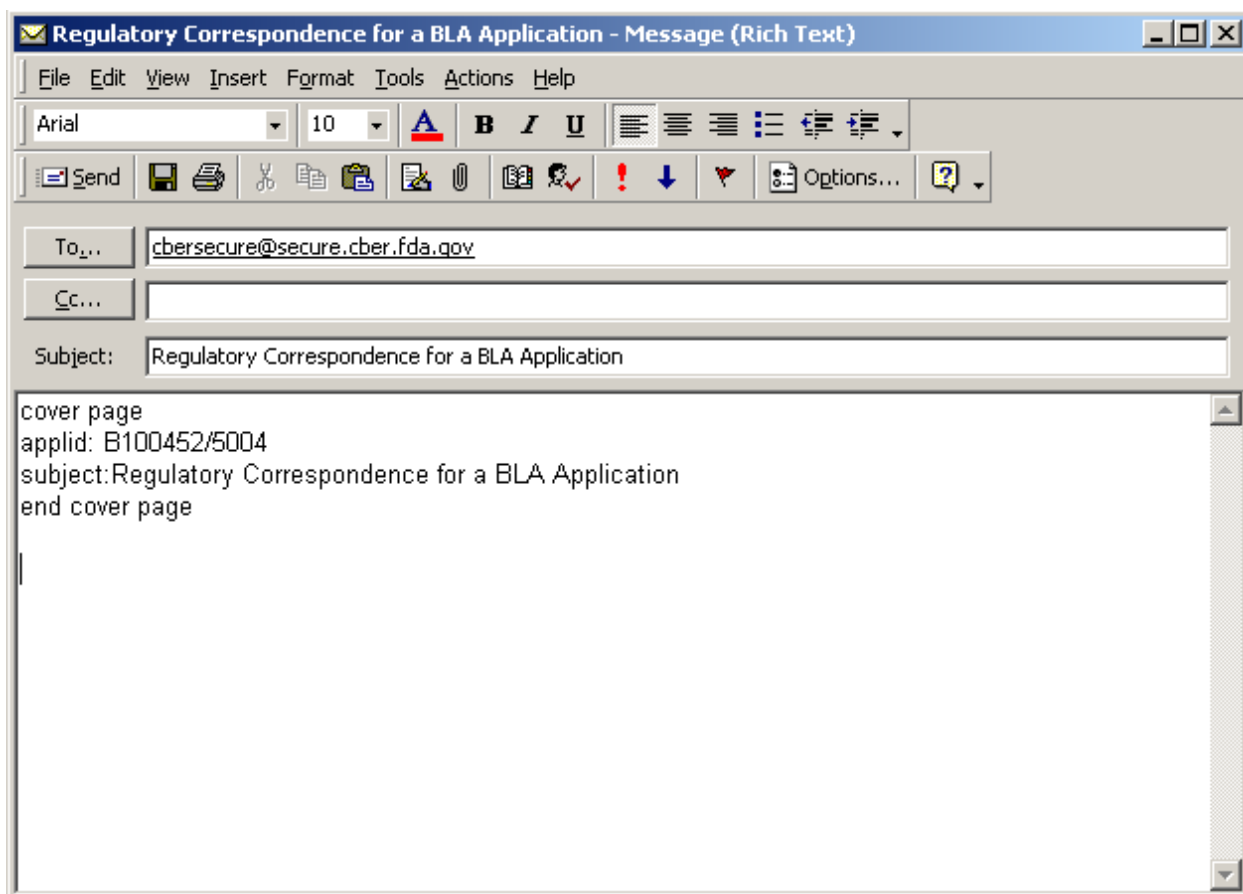
3.1.1 Create Email Message

Open any preferred e-mail program and then create a new email message. ESM will accept messages from any S/MIME compliant email application (e.g., Netscape, Outlook, Lotus Mail). In the **TO:** field, type the following email address: cbersecure@secure.cber.fda.gov.

3.1.2 Cover Page Format

The cover page header must be the first text entered in the message body. The first line of the cover page header should read **'cover page'**. The second line should have the required attribute **'applid'** and on the third line the attribute **'subject'**. For an IND Regulatory Correspondence the applid attribute must contain the IND number preceded by an 'I' (e.g. I3333). For BLA Regulatory Correspondence applid attribute must contain STN of the original submission preceded by a 'B' (e.g. B100452/5004). The subject line should contain information about the Regulatory Correspondence (e.g. Regulatory Correspondence for a BLA Application). The last line of the cover page header should read **'end cover page'**. If the following cover page format is not followed the email message will be sent to the CBER Exchange Server Trouble Folder. Figure 3.1.2-1 depicts a sample cover page for a BLA Regulatory Correspondence.

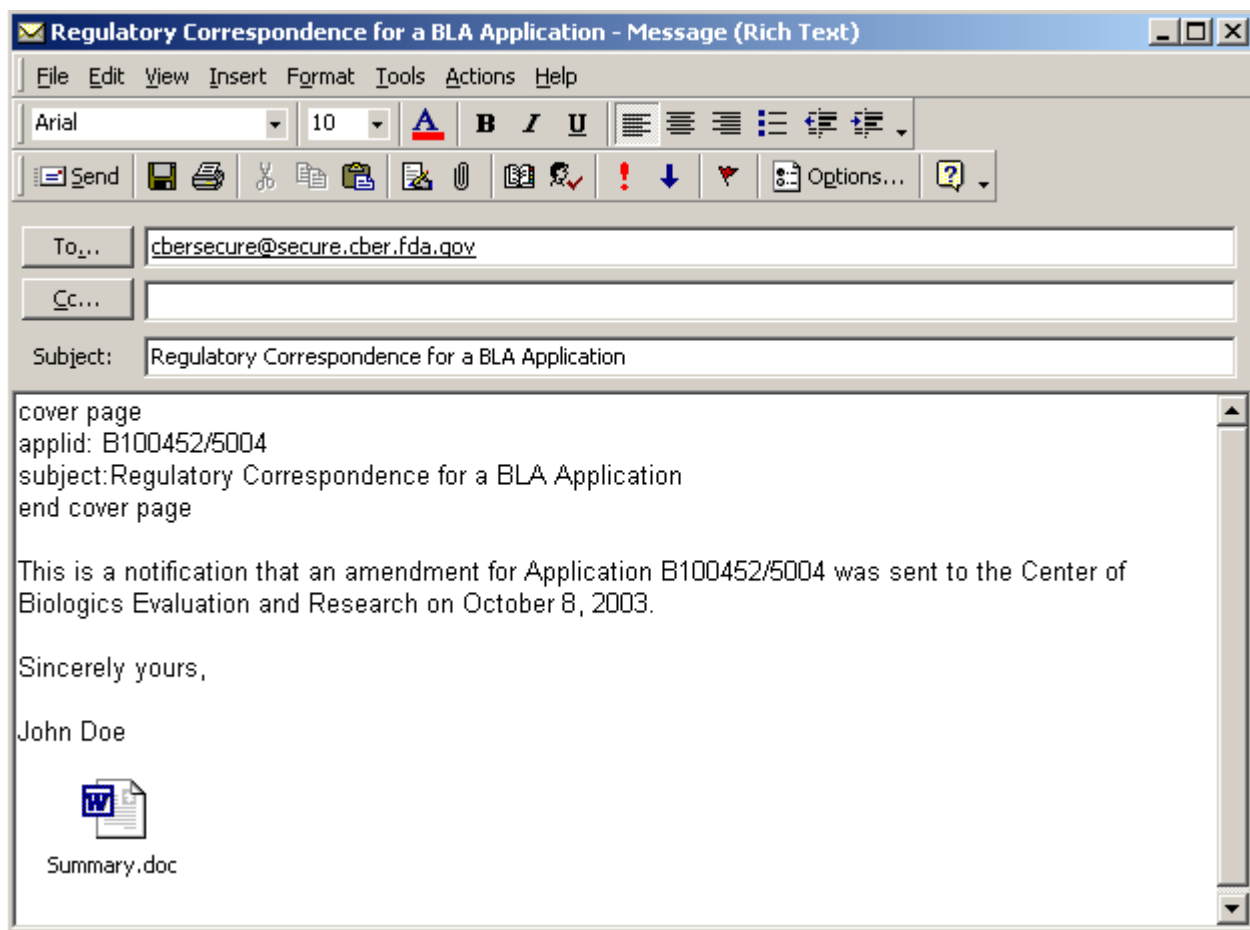
Figure 3.1.2-1-Sample Cover Page



3.1.3 Regulatory Correspondence

Regulatory Correspondence is correspondence between Industry and CBER, which pertains to a submission that has been submitted and received by CBER. The Regulatory Correspondence can be a response to a CBER Letter or a notification about a Submission. Regulatory Correspondence messages may have attachments; however, there are exceptions (See section 3.2). Figure 3.1.3-1 depicts a sample BLA Regulatory Correspondence.

Figure 3.1.3-1-Sample BLA Regulatory Correspondence





3.1.4 Encrypt and Send Email Message

The encryption process varies depending on the technology used to send and receive secure messages. The encryption process is as follows:

- VPN to VPN, the MMS server will automatically encrypt the email message.
- S/MIME to VPN, the message must be encrypted with the sender's public key.

Note: Industry participants registered with CBER may send secure email messages to the cbersecure@secure.cber.fda.gov mailbox. Otherwise, if the secure message is sent to another address, CBER will not successfully receive it.

3.2 ATTACHMENT FILE EXCEPTION LIST

Outlined below is the list of files that should never be submitted as attachments to a Regulatory Correspondence e-mail message. Attaching any of the files listed will prevent the Regulatory Correspondence from being accepted by CBER.

- Form 356h.pdf
- Form 356Hes.pdf (Electronic Version of the 356H.pdf Form)
- Form 1571.pdf
- Form 1571es.pdf (Electronic Version of the 1571.pdf Form)
- Form 3500A.pdf
- Form 3500Aes.pdf (Electronic Version of the 3500A.pdf Form).



4 SECURE MESSAGING CONTACTS

The following names are the points of contact within CBER to answer technical or functional questions:

Technical

Joe Montgomery

CBER EDR/ESM Project Officer

Telephone: 301-827-1332

Greg Dyer

Contractor ESM Administrator

Telephone: 240-314-5542

Functional/Regulatory

Michael Fauntleroy

CBER Director of Electronic Submissions

Telephone: 301-827-5132